REMARKS

Claims 1-18 and 26-35 were pending. Claims 1-10, 13, 15, 17, 26-32 and 34-35 have been cancelled without prejudice to prosecution in another application. Claims 36-37 were added. Therefore, claims 11, 12, 14, 16, 18, 33 and 36-37 are currently pending.

Support for the amended and added claims can be found throughout the specification:

Claim	Location in Specification
11, 14, 16, 33	Page 1, lines 10-15; page 2, lines 23-30; page 3, lines 1-3; page 9, lines 24-25; page 10, lines 1-16;
11 and 16	Page 4, lines 26-27; page 5, lines 1-4; page 5 lines 26-27; page 9, lines 1-10; page 10, lines 17-32;
36	Page 1, lines 15-18; page 2, lines 30-33; page 3, lines 11-14; page 10, lines 3-17;
37	Page 3, lines 1-3.

In the Specification

As requested by the examiner, Figure 1 has been amended. In amended Fig. 1, "HGF" has been changed to "luciferase." Therefore, Applicants request that the objection to the specification be withdrawn in view of this amendment.

Claim Objections

The objection to claims 4, 5 and 27 is moot because these claims are cancelled herein. Therefore, applicants request that the objection be withdrawn.

35 USC § 112, first paragraph

Claims 1-18 and 29-35 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that the specification does not enable administration of any type of nucleic acid molecule encoding HGF or any peptide into the cardiac muscle of a mammal by any route of administration. Applicant respectfully disagrees and requests reconsideration.

The specification enables several exemplary HGF molecules, on page 5, line 26 - page 6, line 10. The specification also provides other non-HGF polypeptides on page 8, lines 25-36. In

addition, several modes of administration are provided, as demonstrated on page 4 of the Office action. However, in order to expedite prosecution, the administration route is clarified as "administering a therapeutically effective amount of a nucleic acid molecule encoding HGF directly to a part of an affected cardiac muscle of a mammal using echocardiographic guidance without thoracotomy." In view of the amendment, Applicants request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

35 USC § 112, second paragraph

Claims 11-18 and 26-35 were rejected under 35 U.S.C. § 112, second paragraph, on the ground that the term "non-invasive" is not definite. Applicant amended the "non-invasive" language to clarify that the HGF nucleic acid molecule is directly administered to a part of an affected cardiac muscle of a mammal using echocardiographic guidance without thoracotomy. In view of this amendment, Applicants request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Claims 4, 5, and 27 were also rejected under 35 U.S.C. § 112, second paragraph. However, these claims have been canceled, so this rejection is now moot.

Claims 11 and 16 were further rejected under 35 U.S.C. § 112, second paragraph, on the ground that the claims are incomplete. Throughout the specification the method is described as a gene therapy method that can be used to treat a disorder (for example see page 1, line 11-18; page 2, lines 20-33; page 3, lines 9-10; page 4, lines 26-27; page 5, lines 1-4; and so on). It is understood by those in the art that gene therapy is effective because following administration of the nucleic acid into a subject, the nucleic acid expresses a therapeutic protein in the treated subject, thereby treating the disorder. Therefore, claims 11 and 16 have been amended to clarify that administration of the nucleic acid treats a disorder by expression of the encoded therapeutic peptide in cardiac muscle. In view of this amendment, Applicants request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Claim 33 was further rejected under 35 U.S.C. § 112, second paragraph, on the ground that the phrase "the affected tissue" did not have antecedent basis. However, this phrase was not used in claim 33. Therefore, Applicants request clarification of this rejection.

35 USC § 102

Claims 1-12, 15, 26-29, 32, 34, and 35 were rejected under 35 U.S.C. § 102(e) as anticipated by Morishita *et al.* (U.S. Patent No. 6,248,722), and provisionally rejected as anticipated by U.S. Application No. 09/660,522 (the '522 application). Claim 11 was amended to clarify that echocardiographic guidance is used to administer the HGF nucleic acid. Because neither Morishita *et al.* nor the '522 application teach or suggest the use of echocardiographic guidance to administer a nucleic acid, these references do not anticipate claim 11 and its dependent claims.

In addition, neither Morishita *et al.* nor the '522 application render the present invention obvious, because there is no teaching or suggestion that echocardiography can be used to administer a nucleic acid. The present Applicants have determined that using echocardiography provides several advantages (see specification, for example page 3, lines 1-10; page 10, lines 3-17; and page 12, lines 32-34). Echocardiographic guidance allows one to administer the gene of interest repeatedly, because the treatment method is relatively non-invasive (it does not require a thoracotomy as in the prior art). Avoiding a thoracotomy is a substantial advantage, because a thoracotomy can result in the loss of intrathoracic negative pressure and collapse of the lung. Thoractomies therefore usually require hospitalization of the subject, and placement of a chest tube to assist with re-inflation of the collapsed lung. In addition, echocardiography allows the heart to be imaged, thereby allowing one to functionally identify the region of the heart in need of therapy and then accurately and directly administer the gene of interest directly into the tissue in need of therapy. The functional identification of the abnormal tissue, combined with the ability to repeatedly administer the therapy without the substantial hazards of a thoracotomy, provide a procedure having substantial benefits not seen with prior approaches. Because neither Morishita *et al.* nor the '522 application disclose or suggest that echocardiographic guidance can be used to administer a nucleic acid less invasively and with greater accuracy, the present invention is not obvious in view of these references. Moreover, neither of these references

disclose administering the nucleic acid under echocardiographic guidance in the absence of a thoracotomy. Hence there is no prima facie case of obviousness.

The rejection of claims 1-10 and 26-28 is moot because these claims are cancelled herein. Therefore, applicants request that the 35 U.S.C. § 102(e) rejection be withdrawn.

Claims 1-12, 15, 26-29, 32, 34, and 35 were rejected under 35 U.S.C. § 102(f) on the ground that the Applicants did not invent the claimed subject matter. As discussed above, neither Morishita *et al.* nor the '522 application teach or suggest the use of echocardiographic guidance to administer a nucleic acid to an affected tissue in the absence of a thoracotomy. Therefore, Applicants request that the 35 U.S.C. § 102(f) rejection be withdrawn.

Claims 1-12, 15, 26-29, 32, 34, and 35 were rejected under 35 U.S.C. § 102(b) as anticipated by WO 97/07824. The Morishita *et al.* U.S. Patent No. 6,248,722 described above, is the § 371 National Stage application of PCT publication WO 97/07824. Therefore, because the specification of WO 97/07824 is identical to Morishita *et al.*, WO 97/07824 does not teach or suggest the use of echocardiography to administer a nucleic acid to an affected tissue. Because WO 97/07824 does not teach all of the elements of the claims, notably the use of echocardiographic guidance, Applicants request that the 35 U.S.C. § 102(b) rejection be withdrawn.

Claims 8-9 were rejected under 35 U.S.C. § 102(b) as anticipated by Hammond *et al.* (U.S. Patent No. 5,792,453), Esakof *et al.* (*Hum. Gene Ther.* 10:2307-14, 1999), and Maurice *et al.* (*J. Clin. Invest.* 104:21-9, 1999). This rejection is now moot because these claims are cancelled herein.

Claims 8-10 were rejected under 35 U.S.C. § 102(b) as anticipated by Aoki *et al.* (*Circulation* 98:I321, 1998). This rejection is now moot because these claims are cancelled herein.

35 USC § 103

Claims 11-14, 16-18, 30 and 31 were rejected under 35 U.S.C. § 103(a) as obvious in view of WO 97/07824 and Esakof *et al.* (*Hum. Gene Ther.* 10:2307-14, 1999). Neither of these references teaches or suggests the use of echocardiographic guidance in the absence of a thoracotomy. Therefore, there is no prima facie case of obviousness. In addition, there are substantial benefits to not using a thoracotomy as described above. Therefore, Applicants request that the 35 U.S.C. § 103(a) rejection be withdrawn.

Claims 11-14, 16-18, 30, 31, and 33 were rejected under 35 U.S.C. § 103(a) as obvious in view of WO 97/07824, Esakof *et al.* (*Hum. Gene Ther.* 10:2307-14, 1999) and Maurice *et al.* (*J. Clin. Invest.* 104:21-9, 1999). Claims 11, 16, and 33 were amended to clarify that echocardiographic guidance in the absence of a thoracotomy is used to deliver the nucleic acid molecules. None of these references teaches or suggests the use of echocardiographic guidance in the absence of a thoracotomy. Therefore, there is no prima facie case of obviousness. In addition, there are substantial benefits to not using a thoracotomy as described above. Therefore, Applicants request that the 35 U.S.C. § 103(a) rejection be withdrawn.

Claims 11-13, 16-18, 30, 31, and 33 were rejected under 35 U.S.C. § 103(a) as obvious in view of WO 97/07824 and Hammond *et al.* (U.S. Patent No. 5,792,453). Applicants respectfully disagree and request reconsideration. Neither WO 97/07824 nor Hammond *et al.* teach the use of echocardiography to administer the therapeutic nucleic acid. WO 97/07824 neither teaches nor suggests the use of echocardiograpy, while Hammond *et al.* only use echocardiography to evaluate ischemic dysfunction before and after administration of FGF-5 (see column 13, line 46-column 14, line 6). That is, Hammond *et al.* are *not* using echocardiography to guide administration of therapeutic nucleic acids. Furthermore, Hammond *et al.* teach the use of an invasive procure (a thoracotomy) to administer the gene therapy agents (see column 13, lines 1-10). This is in contrast to the non-invasive procedure of the present invention, which uses echocardiography to guide administration of the therapeutic nucleic acids directly to the affected muscle. Therefore, because Hammond *et al.* does not teach the use of echocardiography to administer therapeutic molecules, and further teaches an invasive procedure, the present

invention is not obvious in view of WO 97/07824 and Hammond *et al.*. Applicants therefore request that the 35 U.S.C. § 103(a) rejection be withdrawn.

Double Patenting

Claims 11, 12, 15, 29, 32, 34 and 35 were rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1, 2, and 4-6 of U.S. Patent No. 6,248,722. Applicants respectfully request reconsideration. As discussed above, the present claims are directed to a method of treating a disorder, by administering a nucleic acid molecule encoding a therapeutic polypeptide using echocardiography, which is not taught or suggested in U.S. Patent No. 6,248, 722. Therefore, the claimed methods in the present application and those in U.S. Patent No. 6,248, 722 are not obvious variants, and are not co-extensive. Therefore, Applicants request that the double-patenting rejection be withdrawn.

Claims 11, 12, 15, 29, 32, and 33 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over pending claims 7 and 8 of copending Application No. 09/660,522 in view of Maurice *et al.* (*J. Clin. Invest.* 104:21-9, 1999). Applicants respectfully request reconsideration. As discussed above, neither Maurice *et al.* nor the '522 application teach or suggest the use of echocardiographic guidance without thoracotomy to administer a nucleic acid. Therefore, the claimed methods in the present application and those in the '522 application are not obvious variants, and are not co-extensive. Therefore, Applicants request that the double-patenting rejection be withdrawn.

Claims 1-10 and 26-28 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over pending claims 1-11 of copending Application No. 09/856,374. This rejection is now moot because these claims are cancelled herein. Therefore, Applicants request that the double-patenting rejection be withdrawn.

If any questions remain before a Notice of Allowance is issued, the examiner is invited to telephone the undersigned.

Respectfully submitted,

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